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ARCHIVIST

Teratogenicity of first trimester ACE inhibitors

Fetal urine production begins towards the end of the first trimester. Angiotensin converting enzyme (ACE) inhibitors are thought to produce a fetopathy by inhibiting fetal urine production and therefore only do so when taken in the second and third trimesters: the drugs have been considered safe in the first trimester. Features of the fetopathy include renal dysplasia and renal failure, oligohydramnios, hypoplastic calvaria, and intrauterine growth retardation. [Perhaps strangely, if the condition is secondary to fetal anuria or oliguria, they do not seem to include all the features of Potter's syndrome, although pulmonary hypoplasia may, apparently, be a feature]. Now a study in Tennessee (William O Cooper and colleagues. *New England Journal of Medicine* 2006;**354**:2443–51, see also editorial, ibid: 2498–500) has suggested that maternal use of ACE inhibitors in the first trimester increases the risk of major congenital malformations, especially of congenital heart disease and central nervous system (CNS) malformations.

A cohort of 29 507 infants born between 1985 and 2000 included 209 who had been exposed to an ACE inhibitor in the first trimester only, 202 who had been exposed to other antihypertensive drugs in the first trimester only, and 29 096 with no antihypertensive drug exposure at any time in pregnancy. The risk of major congenital malformation was increased significantly, by a factor of 2.7, in the ACE inhibitor group, compared with the no exposure group, but was not increased in the group exposed to other antihypertensives. The risk of cardiovascular malformations was increased 3.7-fold and of CNS malformations 4.4-fold. The numbers of congenital malformations were, however, small and the findings need to be confirmed. The nine children in the ACE inhibitor group with cardiovascular malformations had atrial septal defects, ventricular septal defects, pulmonary stenosis, and patent ductus arteriosus, as either single or combined defects. Three children exposed to ACE inhibitors had CNS malformations, one each with spina bifida, microcephaly plus an eye defect, and coloboma. Two had renal dysplasia.

Maternal medication with an ACE inhibitor in the first trimester is associated with increased risk of a major congenital malformation. ACE inhibitors block the conversion of angiotensin I to angiotensin II. Angiotensin II receptors are widely expressed in fetal tissues and it is suggested that angiotensin II may play a part in the early development of the heart, kidneys, and brain. An editorialist deplores the paucity of available information about the teratogenic risks associated with most drugs and suggests that women who become pregnant while taking an ACE inhibitor should change their medication. Women who have taken an ACE inhibitor in early pregnancy should be offered detailed ultrasonography and echocardiography at 18 weeks gestation.